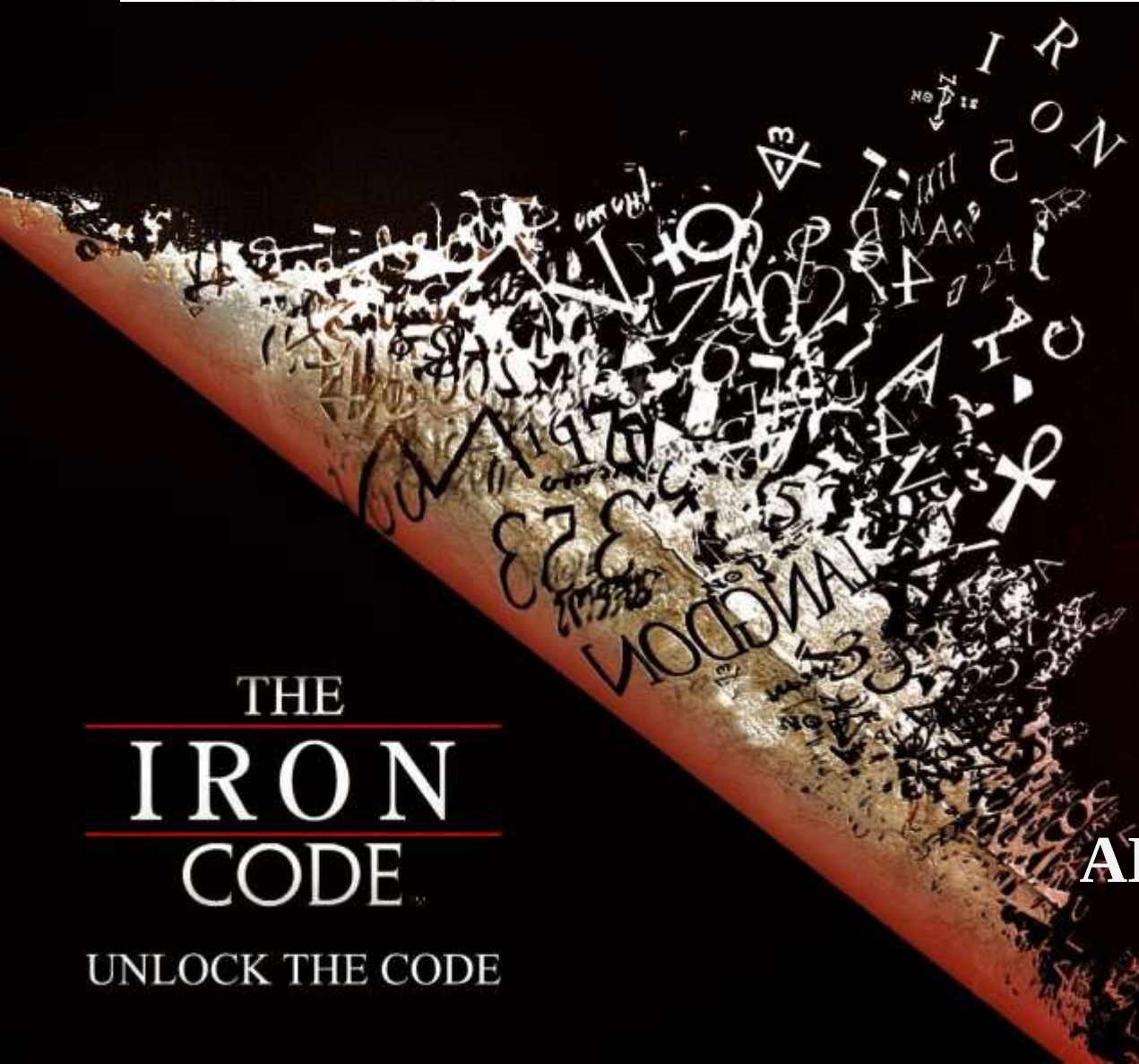
وَأَنزَلْنَا ٱلْحَدِيدَ فِيهِ بَأْسٌ شَدِيدٌ وَمَنَٰفِعُ لِلنَّاسِ



THE IRON CODE

UNLOCK THE CODE

AHMED ELKERAIE

Iron and medicine

- Hundreds of years ago, Hindus from India would roast sheets of iron and then grind them into a fine white powder in oil or milk. This medicine was known as Lauha Bhasma, which would help treat anaemia.

- To this day, the only important use of iron in modern medicine is to help cure iron-deficiency anaemias.

Case

- ESRD on maintenance hemodialysis who is noted to have a Hgb 10.6/TSAT 19%/Ferritin 617/iron 46/TIBC 238/on EPO 4000U/week

- ***What would you do now?***
- Patient EPO decreased to 3000U and started on cosmofer 100 mg x10 doses(1000mg total)
- 1 month later Hgb 11.1 g/dl

- 2 months later: Hgb 10.8/iron 36/TIBC 225/TSAT 16%/Ferritin 1075/on EPO 3000U/week
- ***What would you do in now?***
- Kept patient on current dose of EPO no IV iron given
- One month later Hgb 10.7
- 2 months later: Hgb 9.9/iron 54/TIBC 230/TSAT 17%/Ferritin 706/on EPO 3000U/week
- ***What would you do now?***
- Cosmofer 100 mg x 10 (total 1gram) given and kept on EPO 3000U
- 1 month later: Hgb 10.4
- 2 month later: Hgb 10.2/TSAT 31%/Ferritin 1120/EPO 3000U/week

Why are CKD patients prone to develop iron deficiency?

REDUCED INTAKE

- Poor appetite
- Poor G-I absorption
- Concurrent medication – *e.g. omeprazole*
- Food interactions



INCREASED LOSSES

- Occult G-I losses
- Peptic ulceration
- Blood sampling
- Dialyser losses
- Concurrent meds. – e.g. aspirin
- Heparin on dialysis

Iron Management

WHY..?

-Most common cause of an incomplete response to Epoetin Is iron Deficiency

-Iron is Crucial to the success of Epoetin therapy

-Allow Epoetin to be used more cost-effectively

Iron deficiency stages

Early stage
Iron deficiency syndrome
IDS

Fatigue
Difficulty concentration
Depressed mood
Sleeping disturbance
Neck tensions
Headache
Dizziness
Loss of hair



Late stage
Iron deficiency anemia
IDA

Pallor (pale skin)
General malaise
Muscular weakness
Dyspnea
Palpitation
Tachycardia
Low blood pressure

factors contribute to the development of iron deficiency in CKD

2 g/year



INCREASED LOSSES

- **Occult G-I losses**
- **Peptic ulceration**
- **Blood sampling**
- **Dialyser losses**
- **Concurrent meds. – e.g. aspirin**
- **Heparin on dialysis**

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39 (2 Suppl 1):S1-266.

Type of Iron Dysfunction in HD patients

- Absolute iron deficiency
- Functional iron deficiency
- Inflammatory Block

Absolute Iron Deficiency

- TSAT **falls below 20%** (plasma iron divided by total iron binding capacity x 100)
- Serum ferritin concentration is **less than 200 ng/mL** among hemodialysis patients.

Test	Sensitivity (%)	Specificity (%)
Transferrin Saturation		
<15%	16	88
<18%	58	75
<21%	81	63
<24%	88	44
<27%	92	22
<30%	96	11
Serum Ferritin (ng/mL)		
<50	37	75
<100	48	75
<150	71	69
<200	77	37
<300	90	18
<500	100	0

Fishbane S., J. Am. Soc. Nephrol. 1996 2654-2657

Functional Iron Deficiency

- Characterized by the presence of adequate iron stores as defined by conventional criteria, but an inability to sufficiently mobilize this iron from the liver and other storage sites to adequately support erythropoiesis with the administration of erythrocyte stimulating agents (ESA).

- Serum ferritin level is either normal or elevated, but the TSAT typically is about 20% or less.

- The hallmark of functional iron deficiency is that it responds to iron supplements with an increase in hemoglobin and/or decrease in ESA requirements.

Inflammatory Block or Reticuloendothelial Blockade

- Inflammatory iron block occurs among patients with refractory anemia due largely to an underlying inflammatory state.
- Also characterized with TSAT < 20% and elevated Ferritin 100-800+ ng/ml
- Hepcidin, an acute phase reactant may play a role by preventing the release of iron from macrophages to circulating transferrin.
- Usually does not respond to iron therapy

Functional Iron Deficiency vs. Inflammatory Block

- With functional iron deficiency iron administration will usually increase in hemoglobin and/or decrease in ESA requirements.

- With increasing dose of ESA ferritin levels may decreased with functional but not inflammatory block

- Inflammatory block is most likely present if the weekly administration of intravenous iron fails to result in increased erythropoiesis; instead results in progressive increase in ferritin concentrations.

EBPG KEY RECOMMENDATIONS

All CRF patients must be iron replete to achieve and maintain the target Hb.

Almost all HD patients will require IV iron

EBPG KEY RECOMMENDATIONS

Adequate iron status is defined as :

-Serum ferritin **≥ 100mg/l**

≥ 200mg/l

-TSAT **> 20%**

-Hypochromic RBCs **< 10%**

To achieve this target, the population median will be:

Serum ferritin **= 200-500 mg/l**

-TSAT **= 30-40%**

-Hypochromic RBCs **< 2.5%**

Protocol for dose adjustment

Determine patient Hemoglobin

Hgb≥ 11-12g/dl

Monitor Hgb

If
Serum ferritin **high**
MCH **low**
MCV **low**

Check
CRP for **infection or inflammation**

Hgb< 11-12g/dl

- Check blood pressure
 (if high) control hypertension

- **Check iron stores:**
 -Transferrin saturation ≥ 20%
 -Serum ferritin ≥100ng/ml CKD
 ≥200ng/ml ESRD
- **MCH low in iron deficiency**
- **MCV low in iron deficiency**

Supplement to maintain
Adequate iron levels
In practice we aim for
-Transferrin saturation 30-40%
-Serum ferritin 200-500ng/ml

Initiate Epo therapy

Protocol for dose adjustment

Initiate Epoetin therapy - 50 IU/Kg/week for CKD Predialysis
-150 IU/kg/week for ESRD DIALYSIS

Optimize dose: monitor Hgb and adjust dose accordingly

Hgb 11-12 g/dl

Maintain same dose
Monitor Hgb once/month

Hgb > 12 g/dl &
if Hgb increases >1 g/dl/in any 2 week period

Withhold the Epoetin dose
Monitor Hgb twice a week

Hgb < 11-12 g/dl &
If Hgb increases < 0.7 g/dl/month

Increase weekly dose by 25-50%
Monitor Hgb twice a week
For 2-6 weeks after any dose adjustment

What are the most common causes for Epo resistance

4 Common causes

- **Iron deficiency**
- Infection/inflammation
- Chronic blood loss
- Osteitis fibrosa/hyperparathyroidism

Frequency of iron monitor in CKD patients

Not on Epoetin or IV iron	**3-6 Month**
Initiation phase of EPO and **No** IV iron	**4-6 Weeks**
Initiation phase of EPO and **taking** IV iron	**3 Month**
Maintenance phase of EPO and **taking** iv iron	**3-6 Month**

Previous Guidelines v KDIGO 2011

	Previous Guidelines		KDIGO		
	NICE KDOQI	**ERBP 2008**	**CKD-ND**	**CKD5-PD**	**CKD-5D**
Target Hb range (g/dL)	10.0-12.0	10.0-12.5	10-11.5	10-11.5	10-11.5
Hb to start Iron (Anaemia)	<11		? < 12.0g/dL in women and <13 g/dL in men ? Target no greater than 11.5g/dL unless symptoms		
SF lower limit before iron therapy	≤100	≤100	≤100	≤100	≤200
Target SF	200-500		100-500	100-500	200-500
TS lower limit For iron therapy	≤ 20		≤30	≤30	≤30
Iron replacement if anaemic ESA or no ESA	IV or Oral in CKD-ND and IV in CKD-D	IV or Oral in CKD-ND and IV in CKD-D	Trial oral iron for 1-3 months Single IV dose TDI~1000mg or repeated small doses	Trial of oral iron for 1-3 months IV iron	IV iron Periodic Repletion Dependent on iron status Small doses regularly to maintain iron target

Oral iron therapy

Oral iron salts

- (non-compliance due to GIT upset)
- Intake independent of meals is recommended

Oral Heme iron

- Intestinal iron absorption is 20-30 times more than iron salts
- Minimal GIT upset-more patient compliance

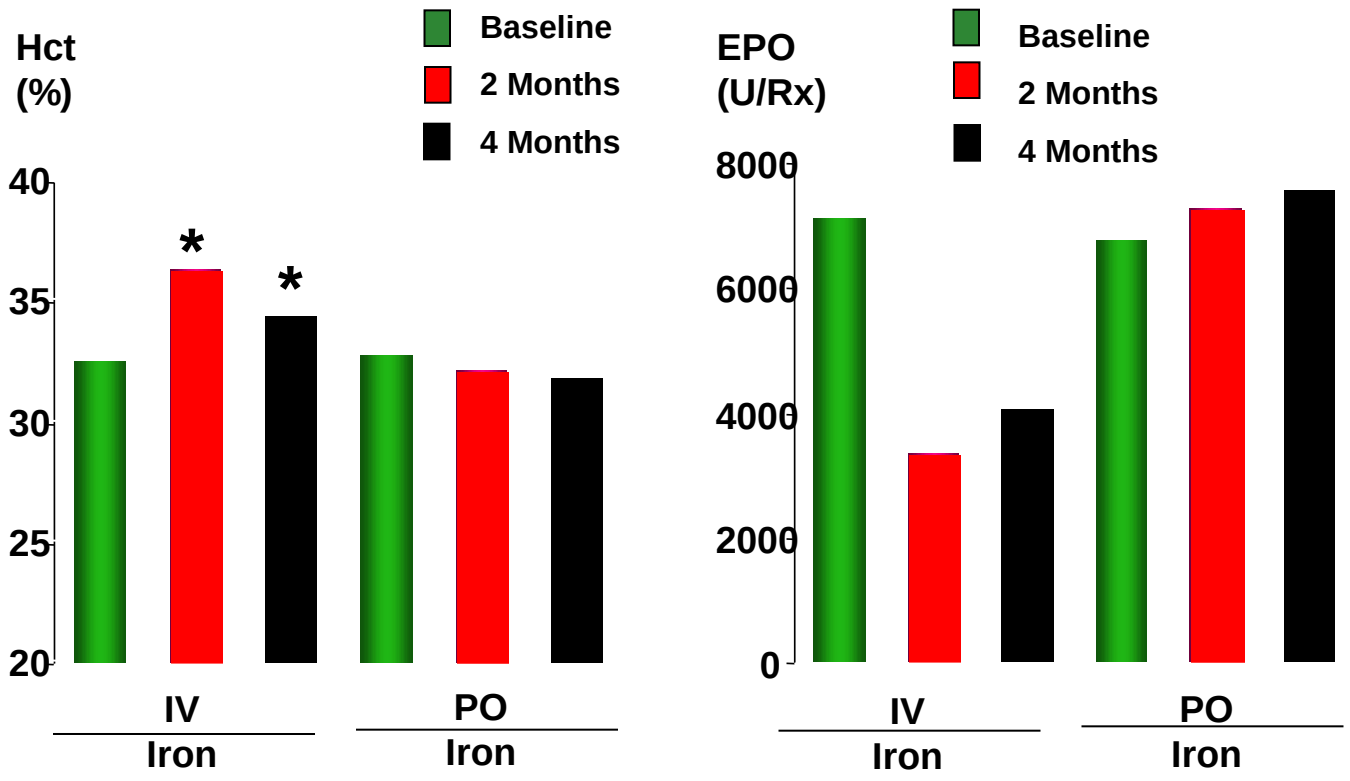


Parenteral iron therapy

- Preparations and administration
 - LMW Iron dextran complex (50 mg iron/ml)
 - Intramuscular and intravenous injection and as total dose infusion (TDI)*
 - Iron sucrose complex (20 mg iron/ml)
 - Only intravenous injection
 - Iron gluconate in sucrose complex (12.5 mg iron/ml)
 - Only intravenous injection

*** Total dose is calculated from the amount of iron needed to restore the haemoglobin deficit and to replenish stores**

Maintenance IV vs. oral iron therapy in hemodialysis patients



Dosage & Administration

Calculation of Iron need:

Total iron need (mg Fe) – Hb in g/l:

- (Body weight (kg) x (target Hb - actual Hb) (g/l) x 0.24) + mg iron for iron stores

 – The factor 0.24 is derived from the following assumptions:

 a) Blood volume 70 ml/kg of body weight ≈ 7% of body weight

 b) Iron content of haemoglobin 0.34%

 – Factor 0.24 = 0.0034 x 0.07 x 1000 (conversion from g to mg).

Short term safety profile

- **Chertow *et al.* (2004),** Studied the relative safety of parenteral iron formulations using data from the US Food and Drug Administration on reported adverse drug events relating to the provision of three formulations of intravenous iron during 1998-2000.

- A total of **21,060,000** doses equivalent to 100 mg IV iron were administered in this period.

- The used parenteral iron formulations were low Mw iron dextran CosmoFer® (used as the reference group), High Mw iron dextran, and Iron gluconate.

Chertow GM *et al.*, Nephrol Dial Transplant 2004; 19: 1571-1575.

Short term safety profile

- The total number of reported parenteral iron-related ADEs was 1981 among ≈ 21,060,000 doses .

- Relative frequency of total ADEs per formulation = reported total ADEs per mill. administered IV doses of 100 mg iron:

- 251 for, and Iron gluconate. (total number of doses 1.0083000)

- 220 for High Mw iron dextran (total number of doses 5.058000)

- ***40 for CosmoFer® (total number of doses 14.919000)***

Fishbane reactions are the most common hypersensitivity reactions to IV iron

- Typically presenting as flushing and/or chest/back pain (myalgia)
- Symptoms abate spontaneously over a few minutes after pausing infusion
- Symptoms typically do not reoccur on re-challenge
- Classified as a mild hypersensitivity reaction

Haematologica 2014; 99(11):1671-76

Factors increasing risk and/or severity of hypersensitivity reactions

- Anxiety (patient or staff)
- Previous reaction to intravenous iron
- History of other drug allergy or allergies
- Severe asthma or eczema
- Mastocytosis
- Systemic inflammatory disease (eg rheumatoid arthritis, lupus)*
- Fast iron infusion rate
- Pregnancy (first trimester)**
- Severe respiratory or cardiac disease
- Treatment with beta blockers, ACE inhibitors
- Old age

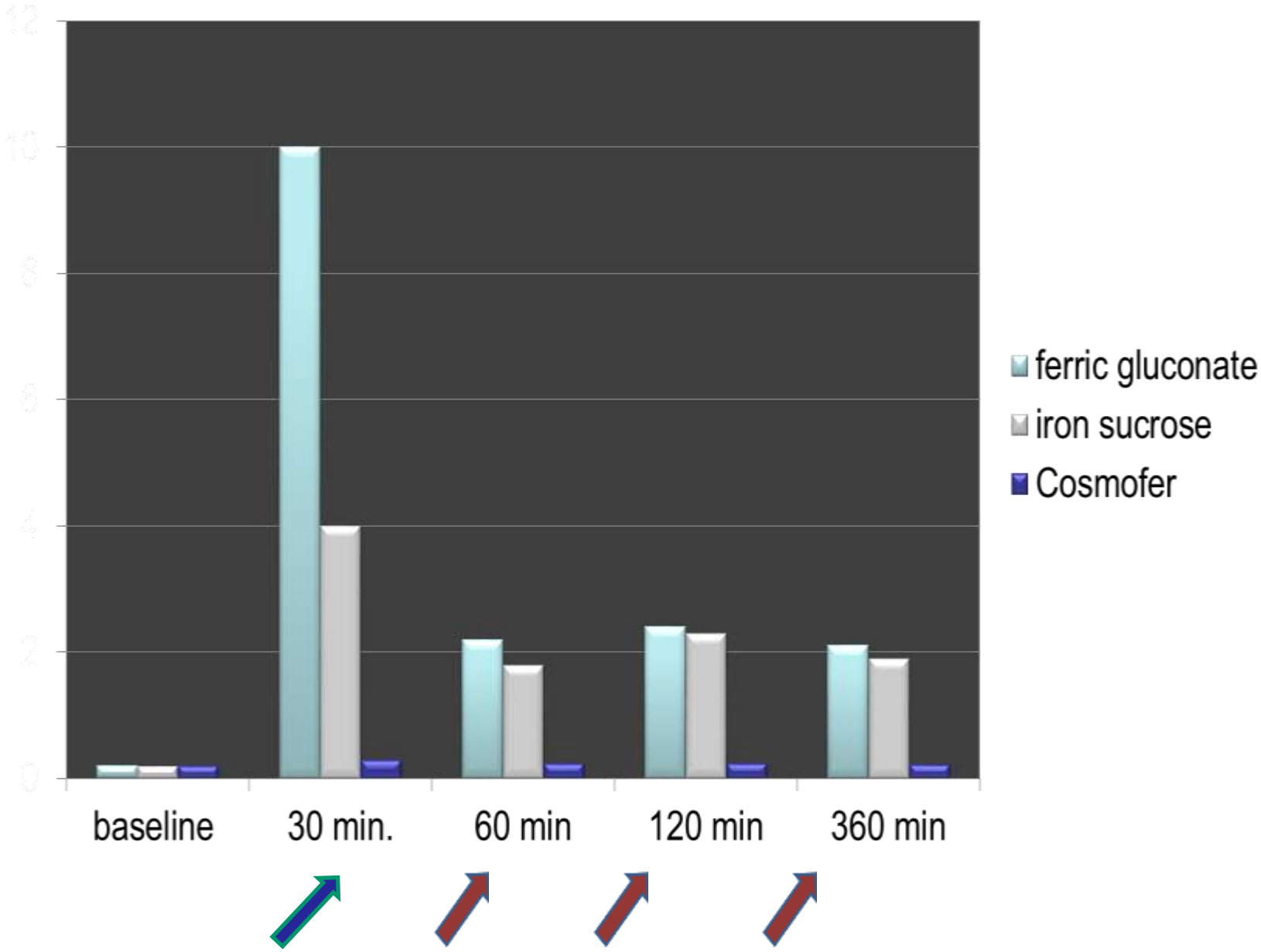
Haematologica 2014; 99(11):1671-76

Long term safety profile
Comparison of Oxidative Stress Markers

Pai *et al.* (2007) published a Comparison of Oxidative Stress Markers After Intravenous Administration of

- Iron Dextran,
- Sodium Ferric Gluconate,
- Iron Sucrose

A B Pai *et al*; Pharmacotherapy 2007:27(3): 343-350


12
10
8
6
4
2
0
baseline
30 min.
60 min
120 min
360 min
ferric gluconate
iron sucrose
Cosmofer

European IV iron safety report

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2013
EMA/549569/2013

Assessment report for: Iron containing intravenous (IV) medicinal products

Procedure under Article 31 of Directive 2001/83/EC

Procedure number: EMEA/H/A-31/1322

Assessment Report as adopted by CHMP with all the information of a confidential nature deleted.

- French medical authorities (ANSM), in December 2011, requested that the EMA assess risk of hypersensitivity with IV irons

- EMA asked all market authorisation holders to provide all their data:
 - Pre-clinical
 - Clinical studies
 - Post-marketing data

Key conclusions

- Benefits of IV iron outweighs risks
- Risk of severe hypersensitivity reactions very low
- Risk exists with every administration
- No differentiation of risk of hypersensitivity could be detected between the IV iron products

European Medicines Agency, Assessment report for: Iron containing intravenous (IV) medicinal products, 13th September 2013. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500150771.pdf Accessed Aug 2014sss

THANK YOU